# Clinical Testing of Preventive Vaccines for Neonates

## An FDA Reviewer's Perspective

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# Objective

- Present general considerations regarding the pre-licensure clinical evaluation of vaccines intended for use in neonates
  - Safety
  - Efficacy
  - Simultaneous vaccination

# Potential Disease Targets for Neonatal Vaccination

| Licensed Vaccines | New Vaccines |
| --- | --- |
| Pertussis | RSV |
| Hib | Parainfluenza virus |
| Pneumococcal | CMV, HSV |
| | HIV |
| | Rotavirus |
| | Meningococcal (conj.) |
| | GBS |

# Vaccines Licensed for Use in Neonates in the U.S.

- Hepatitis B Vaccine (Recombinant)

# Serious Unexpected Adverse Events Associated With Infant Vaccination

- Inactivated RSV vaccine and enhanced disease following natural infection
- High-titer measles vaccine and excess mortality
- Rotavirus vaccine and intussusception

# Pre-clinical Testing of Vaccines Intended for Neonates

- Pre-clinical safety evaluation of vaccines approached on a case-by-case basis
- Pre-clinical models that mimic the human neonatal immune system may be useful in understanding neonatal immune response

# Safety: Progression of Phase 1 and 2 Studies

- Stepwise progression of safety studies from older to younger age groups, down to neonates, in most cases
- Specific approach dependent on vaccine, driven by available safety data, other factors
- Unique safety concerns in neonates may not necessarily be manifested in older age groups (example: live, attenuated intranasal RSV candidate vaccine)

# Designing Studies to Obtain an Adequate Safety Database

- Statistical, clinical, and basic scientific considerations
- Emphasis placed on target population
- Endpoints, size of safety database dependent on vaccine and relevant available data
- Medically attended fever in neonates an important endpoint

# Designing Studies to Obtain an Adequate Safety Database

- Well-documented, standardized monitoring
- Follow-up for at least 6 months after last dose to assess late-onset serious events and chronic conditions
- Randomized, well-controlled studies, evaluated with statistical methods

# Efficacy Evaluation for New Vaccines

- Clinical endpoint trials demonstrating prevention of target disease
- Ideally, efficacy studies are randomized, blinded, controlled
- Size depends on study design and disease incidence
- Foreign efficacy trials may be appropriate, accompanied by safety and immunogenicity data to bridge U.S. and efficacy populations

# Neonatal Indication for Licensed Vaccines: Efficacy Evaluation

- Consider added benefit over current schedule by prevention of disease earlier in infancy
- Use of serological data to support efficacy of new schedule may be appropriate
  - VRBPAC input likely required
  - Non-inferiority relative to current schedule
  - Does earlier immune response translate into substantial disease reduction in young infants?
  - Immunogenicity evaluation after each dose?
  - Antibody decay over time

# Effect of Maternal Antibody on Neonatal Immune Response

- Study population ideally representative of target population with regard to patterns of maternal immunity
- Differences in pre-immunization antibody levels between study groups need to be accounted for in analyses
- Changing patterns of maternal immunity

# Evaluation of Neonatal Immunization in the Context of the Current Immunization Schedule

- Immunogenicity and safety data to support simultaneous administration with licensed vaccines
- Early evaluation of potential immunological interference
- Potential for tolerance induction and carrier-induced immune suppression
- Impact of neonatal vaccination on safety of current vaccination schedule

# Conclusions

- Prospects for neonatal vaccination present new challenges for evaluation of safety, efficacy, and effect on current immunization schedule
- Standards for safety and efficacy flexible, product-specific, dependent on benefit-to-risk considerations
- Importance of communication between sponsors and FDA reviewers

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